mRNA technology could be possible treatment for rare liver genetic disease

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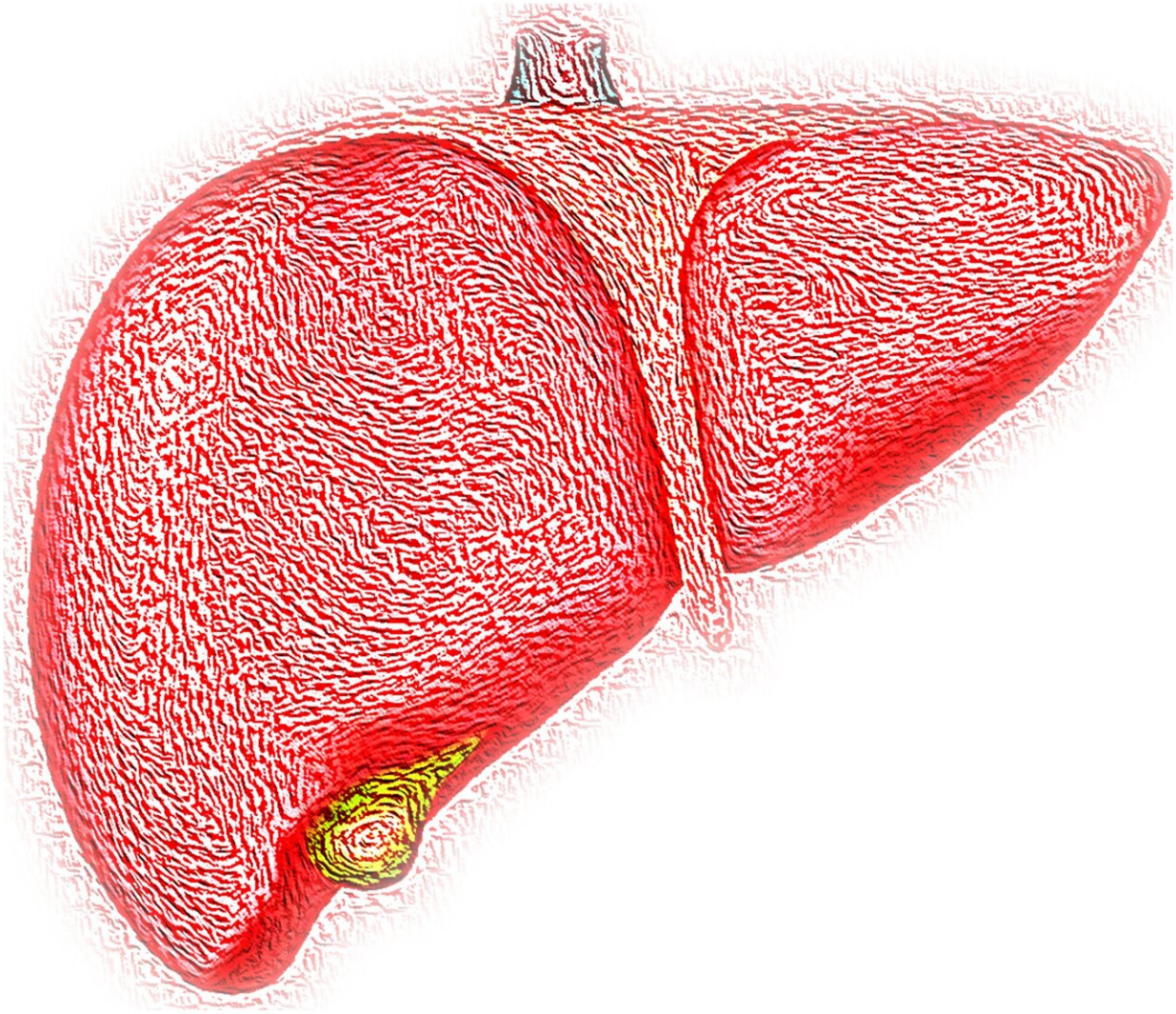

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By exploiting the technology used in COVID-19 vaccines, a team led by UCL, King's College London and Moderna scientists has created an effective therapy for a rare disease, in a study in mice, demonstrating the technology's potential therapeutic use in people.

The research, published in *Science Translational Medicine*, found that messenger RNA (mRNA) could be used to correct a rare liver genetic disease known as argininosuccinic aciduria in a mouse model of the disease.

Argininosuccinic aciduria is an inherited metabolic disorder that affects how the body breaks down protein—potentially leading to high levels of ammonia in the blood. Patients affected by the disease are found to also experience an imbalance of glutathione regulation, which is important for liver detoxification. The condition occurs in approximately one in 100,000 newborns.

Over the coming years, the team aims to trial the therapy in people. Messenger RNA therapies are also currently being investigated in other rare inherited metabolic diseases—propionic and methylmalonic acidemias—in global clinical trials sponsored by Moderna, including at Great Ormond Street Hospital for Children.

Co-lead Principal Investigator, Dr. Julien Baruteau (UCL Great Ormond Street Institute of Child Health), said, "Messenger RNA has revolutionized the field of vaccines during the COVID-19 pandemic. We believe it can now do the same for rare diseases."

Rare diseases usually result from errors in the patient's DNA and affect

around 300 million people worldwide.

However, fewer than 5% of these conditions have approved therapies. Most of these treatments use gene therapy to switch out the faulty gene and replace it with a normal functioning one, to alleviate the disease.

Until recently, gene therapy employed modified viruses to bring the therapeutic gene to the disease cells. However, these viral systems can cause severe adverse effects, such as reactions from the patient's own immune system, meaning that they can't be rolled out widely.

Consequently, the team wanted to investigate the possibility of using mRNA technology as an alternative solution.

Messenger RNA is a molecule that contains instructions that direct the cells to make proteins. By protecting the mRNA in a microdroplet of lipids, scientists were able to inject the mice intravenously with the therapy and target their liver cells.

The researchers tested the therapy on 31 mice both from birth and at a late stage of the disease as a rescue therapy in older mice that had argininosuccinic aciduria. They also used an equal number of untreated mice as a control (comparison) group.

For the mice, the benefit of each mRNA treatment only lasted around seven days, so the procedure was performed weekly over the course of up to eight weeks. However, the researchers expect that translation to humans will allow for longer gaps between treatments.

Over the course of the trial, the mice were given positron emission tomography (PET) scans as a non-invasive way to track the correction of glutathione regulation and the success of the treatment.

Researchers found that the treatment corrected the lethal consequences of the disease. All mice with the disease at birth left untreated died within the first two weeks of life, while the mice that received the mRNA treatment at birth survived for over three months. Additionally, six out of seven mice who received mRNA treatment as rescue therapy survived, while all those that were left untreated died.

The researchers also noted that, mRNA-treated organs were very similar to those in the unaffected, control mice.

Dr. Baruteau said, "We have shown that mRNA holds an unprecedented therapeutic potential for incurable genetic diseases, in particular liver conditions. We aim to apply this approach to other inherited liver diseases and translate mRNA therapy to patients, especially in children."

Dr. Tim Witney, Co-lead PI (School of Biomedical Engineering & Imaging Sciences, King's College London), said, "This is a great example of collaborative science across multiple areas of expertise, which has yielded remarkable results. By understanding what goes wrong in this disease, we can not only correct the error, but follow this correction in real-time using imaging. We are looking forward to bringing these advances to patients in the near future."

Dr. Paolo Martini, Chief Scientific Officer for International Therapeutics Research Centers at Moderna, said, "This collaboration has exemplified how academia and industry can work in synergy to explore how mRNA technology can be harnessed against rare diseases and may potentially lead to a treatment for a severe and debilitating disease such as argininosuccinic aciduria."

More information: Sonam Gurung et al, mRNA therapy corrects defective glutathione metabolism and restores ureagenesis in preclinical argininosuccinic aciduria, *Science Translational Medicine* (2024). DOI:

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